REMARKS

Attorney for Applicants has carefully reviewed the outstanding Office Action on the above-identified application. Applicants have amended the application, as set forth herein, and respectfully submit that the application, as amended, is in condition for allowance.

Applicants have amended claims 2 and 28 and cancelled claim 13 to overcome the rejections cited in the Office Action under Section 112, second paragraph. Claims 2 and 28 was amended so that the term "vector" has antecedent basis, the term "it" was removed from these claims, and minor matters of form were corrected. With these amendments, Applicants respectfully submit that claims 2 and 28 are in condition for allowance. Applicants have also amended claims 4, 8, 42, and 43 to correct minor matters of form.

Applicants' claimed invention relates to a method and apparatus for fractionating charged macro-molecules, such as DNA, using asymmetric electric fields applied to a matrix of obstacles. Molecules to be fractionated are introduced into the matrix and are fractionated according to size along a horizontal direction of the matrix. The asymmetric fields include alternating first and second electric fields oriented at an angle with respect to each other. Durations and intensities of the first and second electric fields are varied such that one field is stronger in duration or intensity than the other field, or is otherwise asymmetric. The alternating first and second electric fields fractionate the molecules according to size. The separated molecules are collected at a plurality of locations along the bottom edge of the matrix, allowing for continuous fractionation.

Applicants have amended claims 1, 18, and 27 to overcome the rejections cited in the Office Action of claims 1-46 as being obvious over U.S. Patent No. 6,027,623 to Ohkawa in view of U.S. Patent No. 4,830,726 to Stamato, et al.

Ohkawa discloses a device and method for electrophoretic fractionation of molecules in a fluid medium using a plurality of obstacles arranged on a substrate in rows and columns. Each obstacle includes inclined walls with respect a fluid channel, and a uniform electric field can be applied to the device. As molecules diffuse through the device, the walls of the obstacles re-direct the molecules back into the same fluid channel. Faster-diffusing, smaller molecules migrate through the channel first, followed by slower-diffusing, larger molecules.

Stamato, et al. discloses a method for separating DNA molecules by gel electrophoresis, using alternating applications of high and low strength electric fields in opposite directions. The high strength field is maintained for a shorter interval than the low strength field, and net migration of DNA molecules occurs in the direction of the low strength field.

Neither Ohkawa nor Stamato, et al., taken alone or in combination, teach or suggest each element of Applicants' claimed invention, as set forth in amended claim 1. Specifically, neither of these reference, taken alone or in combination, teach or suggest providing a method of **continuously** fractionating charged macro-molecules comprising the steps of loading molecules into a matrix of obstacles; **applying an asymmetric electric field to the matrix to separate the molecules according to size along a horizontal direction of the matrix; and collecting separated molecules at a plurality of locations along a bottom edge of the matrix**, as set

forth in amended claim 1. Ohkawa fails to teach or suggest applying asymmetric fields to a matrix to separate molecules according to size along a horizontal direction of the matrix, nor does Ohkawa teach or suggest collecting separated molecules at a plurality of locations along a bottom edge of the matrix. Rather, Ohkawa merely provides for fractionation based on different diffusion rates, wherein diffused molecules emerge at the same location at different times depending upon sizes of the molecules. Ohkawa further teaches that each obstacle has "a left front wall and a right front wall, said front walls being symmetrical to each other and respectively inclined to redirect macromolecules diffused from one said fluid channel back into said same fluid channel during migration of the macromolecules." Moreover, Ohkawa teaches the use of low fields in order to allow for diffusion. In contrast, the present invention does not rely on diffusion, and does not require the specific obstacles described in Ohkawa. As such, Ohkawa and is incapable of providing continuous fractionation.

Stamato, et al. fails to remedy the deficiencies of Ohkawa. While Stamato, et al. discloses applying alternating electric fields in opposite directions to fractionate molecules, Stamato, et al. is devoid of any teaching, suggestion, or motivation to separate macro-molecules according to size using asymmetric fields and collect separated molecules at a plurality of locations along a bottom edge of a matrix, as set forth in amended claim 1. Moreover, the combination of Ohkawa with Stamato, et al. would result in a device that is incapable of continuously fractionating macro-molecules as achieved by the present invention, wherein molecules are introduced at a source, are separated according to size along a horizontal direction of the matrix by application of asymmetric electric fields, and are collected at a plurality of locations to allow for continuous fractionation of molecules. Accordingly, Applicants

respectfully submit that claim 1 and claims 2-17, which depend from claim 1 and contain all of the limitations thereof, are patentable over Stamato, et al. in view of Ohkawa.

Neither Ohkawa nor Stamato, et al., taken alone or in combination, teach or suggest each element of Applicants' claimed invention, as set forth in amended claim 18. Neither of these reference, taken alone or in combination, teach or suggest providing a method of **continuously** fractionating charged macro-molecules comprising the steps of loading molecules into a matrix with an array of obstacles; applying to the matrix electric fields whose amplitudes are constant in time; **varying field orientations of the electric fields with time to create an asymmetrical electric field to separate the molecules according to size along a horizontal direction of the matrix; and collecting separated molecules at a plurality of locations along a bottom edge of the matrix**, as set forth in amended claim 18. Ohkawa, discussed earlier, fails to teach or suggest applying asymmetric fields to a matrix to separate molecules according to size along a horizontal direction of the matrix and collecting separated molecules at a plurality of locations along the bottom edge of the matrix. Stamato, et al. similarly fails to teach or suggest separating molecules according to size along a horizontal direction of the matrix and collecting separated molecules at a plurality of locations along a bottom edge of a matrix. As such, Applicants respectfully submit that claim 18 and claims 19-26, which depend from claim 18 and contain all of the limitations thereof, are patentable over Stamato, et al. in view of Ohkawa.

Finally, Applicants respectfully submit that neither Ohkawa nor Stamato, et al., taken alone or in combination, teach or suggest each element of Applicants' claimed invention, as set forth in amended claim 27. Neither Ohkawa nor Stamato, et al., taken alone or in combination,

teach or suggest providing an apparatus for **continuously** fractionating charged macro-molecules comprising an array of obstacles; **asymmetrically alternating electric fields applied to the array of obstacles to separate molecules according to size along a horizontal direction of the array; and a plurality of locations along a bottom edge of the array for collecting separated molecules**, as set forth in amended claim 27. Ohkawa fails to teach or suggest continuously fractionating molecules by applying asymmetrically alternating fields to a matrix to separate molecules according to size along a horizontal direction of the matrix, and collecting separated molecules at a plurality of locations along a bottom edge of the matrix. Stamato, et al. similarly fails to teach or suggest continuously fractionating macro-molecules by applying asymmetric alternating electric fields to a matrix to separate the molecules according to size along a horizontal direction and collecting separated molecules along a bottom edge of the matrix. As such, Applicants respectfully submit that claim 27 and claims 28-46, which depend from claim 18 and contain all of the limitations thereof, are patentable over Stamato, et al. in view of Ohkawa.

All issues raised in the Office Action are believed to be addressed. Claims 1, 2, 4, 8, 18, 27, and 28 were amended, and claims 13, 14, 22, 23, and 41 were cancelled. Claims 1-12, 15-21, 24-40, and 42-46 are pending in this application, and are believed to be in condition for allowance. No new matter is believed to have been added. Re-examination is requested and favorable action solicited.

Respectfully submitted,

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